

ABSTRACT

Anorexigenic neuropeptides have the potential to decrease food intake and ameliorate obesity and its complications such as high blood glucose or high blood pressure. However, they are not able to cross the blood-brain barrier after peripheral application. Recently, we have designed and synthesized lipidized analogs of prolactin-releasing peptide (PrRP), which resulted in stabilization of the molecule and allowed us to apply the peptide to the periphery to achieve its central biological effect, as it was demonstrated by increased neuronal activity shown by c-Fos in particular hypothalamus nuclei.

The aim of this study was to choose the effective dose in acute food intake experiments and then to characterize the subchronic effect of palmitoylated PrRP analogs in mouse and rat models of obesity and diabetes. Several animal models were used: diet-induced obese (DIO) mice (C57Bl/6J), DIO Sprague-Dawley rats, and two rat models with leptin receptor-deficiency: Zucker diabetic (ZDF) rats and spontaneously hypertensive (SHROB) rats.

Consumption of a high-fat diet in DIO mice and rats increased their body weight and blood pressure. Two-week intraperitoneal treatment with palmitoylated PrRP31 lowered the food intake, body weight, and returned the blood pressure to normal levels. This treatment also improved glucose tolerance in DIO rats. In contrast, in ZDF and SHROB rats, the same treatment lowered the food intake but did not significantly affect the body weight, probably because of severe leptin resistance that was likely due to a non-functional leptin receptor. However, the treatment improved glucose tolerance and reduced blood insulin levels in the SHROB model and tended to improve glucose tolerance in the ZDF model, suggesting that functional leptin is required for the anorexigenic but not for the antidiabetic effects of palmitoylated PrRP31.

Our data showed a good efficacy of lipidized PrRP31 in animal models of obesity and related metabolic complications. Thus, the strong anorexigenic, body weight-reducing and blood glucose-improving effects make palmitoylated PrRP an attractive candidate for anti-obesity and glucose-lowering treatments.